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Nocturnal cardiac autonomic profile in young primary insomniacs and good sleepers

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ABSTRACT

We investigated cardiac vagal and sympathetic activity in 13 young primary insomniacs (PI; 24.4 ± 1.6 years) and 14 good sleepers (GS; 23.3 ± 2.5 years) during nocturnal sleep. Pre-ejection period (PEP; inversely related to beta-adrenergic sympathetic activity), interval between consecutive R-waves (RR), and vagal-related indices of time- and frequency-domain heart rate variability were computed during pre-sleep wakefulness and undisturbed arousal-free sleep stages (N2, SWS, REM) as well as across the whole night irrespective of the presence of disruptive sleep events (e.g. sleep arousals/awakenings) and/or sleep stage transitions. Groups exhibited a similar vagal activity throughout each undisturbed sleep stage as well as considering the whole night, with a higher modulation during sleep compared to prior wakefulness. However, PEP was constantly shorter (higher sympathetic activity) during pre-sleep wakefulness and each sleep stage in PI compared to GS. Moreover, pre-sleep RR intervals were positively associated with sleep efficiency and negatively associated with wake after sleep onset in PI. Altogether our findings indicated a dysfunctional sympathetic activity but a normal parasympathetic modulation before and during sleep in young adults with insomnia.

1. Introduction

Converging data support the link between insomnia and cardiovascular (CV) disease (Spiegelhalder et al., 2010). A growing body of evidence supports the association between insomnia and adverse CV events (Chien et al., 2010; Lanfranchi et al., 2009; Laugsand et al., 2011; Rosekind and Gregory, 2010) and it is well known that overstress of the CV system, i.e. elevated resting blood pressure (Vasan et al., 2001), heart rate (Cooney et al., 2010; Fox et al., 2007), sympathetic hyper-activity (Hamer and Malan, 2010) and autonomic imbalance (Thayer et al., 2010), plays an important role in enhancing the risk for adverse outcomes. Insomnia, therefore, is recognized as a risk factor for developing CV diseases with a risk ratio comparable to the major and well known risk factors such as smoking, hypertension, obesity, and diabetes (Spiegelhalder et al., 2010). Given that insomnia is a major public health problem affecting millions of individuals with a prevalence rate up to 10% in its chronic form (National Institutes of Health (NIH), 2005), it is critical to determine the underlying causes and correlates of CV disease in insomnia. In spite of evidence from epidemiological studies linking insomnia and cardiovascular disease (Lanfranchi et al., 2009; Laugsand et al., 2011; Rosekind and Gregory, 2010; Spiegelhalder et al., 2010), few studies have investigated nighttime autonomic nervous system (ANS) functioning in primary insomniacs (PI). Vagal influence on the heart can be noninvasively assessed by time-domain HRV indices (Camm et al., 1996), like the square root of the mean squared difference of beat-to-beat intervals (RMSSD), the percentage of adjacent beat-to-beat intervals changing >50 ms (pNN50) and frequency-domain heart rate variability (HRV) absolute power in the range of 0.15–0.4 Hz (high frequency, HF).

Focusing on the HRV frequency-domain, activity that occurs between 0.04 Hz and 0.15 Hz (low frequency, LF) is still debated, with some studies defining it as a marker of sympathetic activity (see Montano et al., 2009), but others considering it as an index of both sympathetic and parasympathetic modulation (Berntson et al., 1997). However recent reports have challenged this view, considering LF fluctuations being predominantly the expression of vagal activity involved in the control of blood pressure (Billman, 2013; Reyes del Paso et al., 2013). Given this difficulty to determine *what* exactly the LF reflects, the meaning of the LF/HF ratio, an extensively used index which was supposed to reflect the sympatho-vagal balance (i.e. the balance

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between the two branches of the ANS), has also been debated (Billman, 2011, 2013).

Instead of using the controversial LF component of HRV, cardiac-sympathetic activity can be non-invasively measured by the pre-ejection period (PEP), a validated impedance cardiography (ICG) index indicating the time of the left ventricular electromechanical systole, controlled by beta-adrenergic mechanisms and inversely related to ANS activity (Schächinger et al., 2001; Sherwood et al., 1990).

Notwithstanding these important methodological issues, previous studies employing HRV method reported an overnight increase in LF and reduction in HF power (Bonnet and Arand, 1998), and SDNN (Spiegelhalder et al., 2011) in PI compared to healthy sleepers, suggesting an overall reduced HRV and vagal-related activity in PI.

However, others failed to find any group differences in these measures (de Zambotti et al., 2013; Jurysta et al., 2009). Moreover, Varkevisser et al. (2005) failed to find a significant difference in PEP, whereas previous data from our laboratory suggested a constant nocturnal sympathetic hyper-activation (short PEP) during the immediate sleep onset period (de Zambotti et al., 2011) and throughout the whole night in young PI compared to good sleepers (de Zambotti et al., 2013).

A recent study performed HRV analysis on selected artifact-free 5-min periods sampled across the night in PI and controls (Farina et al., 2014); a single bin was analyzed for each of the following condition: "pre-sleep wake", "early light sleep", "slow wave sleep", "REM sleep", "early and late N2 sleep", as well as "post-sleep wake". PIs had a faster HR but few differences in HRV variables compared to controls: LF power (calculated in normalized units) was increased in pre-sleep wake and LF/HF ratio was elevated in early N2 sleep in PI compared to controls; surprisingly, PI showed an unexpected elevated total and high frequency HRV in early N2 sleep compared to controls.

Summarizing, results investigating cardiac ANS functioning in PI are inconsistent. Overall, studies adopting the HRV technique have provided some evidence of a shifting in sympathovagal balance toward sympathetic dominance in PI. However, the analysis of HRV does not allow the possibility of directly assessing the sympathetic modulation of the heart, particularly during sleep when vagal modulation is predominant (Trinder et al., 2012). Other challenging methodological issues contribute to the inconsistencies in findings, including: how periods of analysis for HRV are selected (the presence of arousals/awakenings, and/or sleep stage transitions has not always been considered), the definition of insomnia (ranging from a self-reported definition to a clinical diagnosis, considering or not the presence of objective short sleep duration (see Vgontzas et al., 2013)), and the confounding effect of age and age-related issues on HRV (Antelmi et al., 2004).

Here, we aimed to further assess ANS functioning in primary insomniacs and to confirm previous findings of our lab (de Zambotti et al., 2013). To accomplish our aim, we investigated ANS activity in a larger and independent sample of young PI compared with healthy good sleepers (GS) employing frequency- and time-domain HRV analysis and ICG in artifact-free sleep stages determined by polysomnography as well as during the whole night irrespective of sleep stage transitions and disruptive sleep events. Also, we aimed to explore the nocturnal time-course of time-domain vagal-related indices, which are mainly influenced by the circadian system (Burgess et al., 1997), in insomniacs compared to GS. The advantage in combining HRV analysis and ICG allowed us to measure pure indices of vagal (HF power, RMSSD, pNN50) and sympathetic (PEP) activity, together with indices reflecting total HRV (SDNN and total power).

2. Material and methods

2.1. Participants

Potential participants were recruited through flyers, announcements or advertisements at the Universities of Padua, and evaluated by screening interviews to ensure that they met eligibility criteria. PI and NS had to meet, respectively, the *Research Diagnostic Criteria for Primary Insomnia and Normal Sleepers* (Edinger et al., 2004). More than 100 undergraduates were screened over a period of one year. Thirty insomniacs were potentially eligible. Three of them were excluded for taking hypnotics, 9 for being at risk for depression, and 5 of them had an irregular sleep/wake schedule. Thirteen PI (8 women) and 14 GS (7 women) made up the final sample.

PI had to complain of difficulty initiating sleep and/or maintaining sleep, and/or non-restorative sleep. In addition, nocturnal symptoms should impact daytime functioning. Both nocturnal and diurnal symptoms should occur for at least one month and be independent of another medical and/or mental condition. They also had to score ≥ 5 on the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and ≥ 11 on the Insomnia Severity Index (ISI) (Morin, 1993). GS had to report lower scores than these cut-offs, no complaints of unsatisfactory sleep, report a regular sleep/wake schedule and not suffer from any sleep disorders or sleep disruption due to medical and/or mental conditions. Exclusion criteria for both groups were body mass index (BMI; kg m^{-2}) ≥ 30, extreme chronotypes assessed using the Morningness–Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976), current medical and/or psychiatric conditions, and shift work or time-zone travel in the six months prior to the study. All participants were non-smokers. The usual average daily consumption was low for alcohol (less than 12 g/day) and caffeine or energetic beverages (less than 200 mg/day) in both PI and GS. No participants reported ever using drugs affecting sleep and/or CV system (e.g. anxiolytics, antidepressants, hypnotics, and benzodiazepines) and all participants were drug free at the time of the experiment.

The usual sleep times of participants were similar (± 1 h) to the experimental sleep schedule, as assessed by daily sleep diaries completed for one week before the experiment. Participants gave written informed consent. The study protocol was approved by the Ethics Committee of the University of Padua.

Demographics and subjective screening measures are provided in Table 1.

2.2. Procedure

Participants spent two consecutive polysomnographic (PSG) nights (adaptation/screening and experimental) at the sleep laboratory of the University of Padua. Participants were instructed not to drink beverages containing alcohol, caffeine or other stimulants during the 24 h prior to each night. They arrived at the laboratory at the scheduled time (8 pm) and the electrodes were attached. Time in bed was fixed from 12 pm (lights-out) to 8 am (lights-on). The adaptation/screening PSG night confirmed no further sleep disorders. Only data from the experimental nights were analyzed.

2.3. PSG assessment

PSG recordings were made with Compumedics Siesta 802 (Compumedics, Abbotsford, Australia) using electroencephalography (EEG), electrooculography and electromyography according to the American Academy of Sleep Medicine (AASM; Iber et al., 2007) guidelines. EEG signals were amplified, band-pass filtered (0.3–35 Hz) and digitalized at 512 Hz. Arousals and stages (Wake, N1, N2, SWS and REM) were scored according to AASM criteria (Iber et al., 2007). Time in bed (TIB; min) was fixed (480 min for all participants). Total sleep time (TST; min), sleep efficiency (SE, as TST / TIB $\times$ 100; %), sleep onset latency (SOL, defined as the time from lights-out to the first epoch of sleep; min), rapid-eye-movement latency (REML, defined as the time from the sleep onset to the first epoch of REM, min), wake after sleep onset (WASO, min), the arousal index (ArI, number of arousals times 60 divided by TST), and percentage of time spent in each sleep stage of sleep were calculated.